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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/302,434	04/30/1999	KLAUS BOSSLET	026083/0119	6895

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/302,434	BOSSLET ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-43,47,54-58,66 and 67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-43,47,54-58,66 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed June 26, 2003 (Paper No. 27) is acknowledged. Claims 37, 66 and 67 were amended.

2. Claims 37-43, 47, 54-58, 66 and 67 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

4. The rejection of claim 42 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn upon further consideration in view of the fact that claim 42 depends from claim 37, which limits the nature of the exposed carbohydrate residue.

5. The objection to claim 47 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn. However, see new rejection under 112, 1st paragraph.

Claim Rejections Maintained:

6. The rejection of claims 37, 58, 66 and 67 under 35 U.S.C. 103(a) as being unpatentable over Seemann (EP 501,215; published Feb. 9, 1992; cited in the IDS; German language) as evidenced by Derwent database English language abstract; in view of Mattes (Mattes, M.J., Journal of the National Cancer Institute, 79(4): 855, 1987; cited in IDS) is maintained for the reasons of record. Applicant's arguments have been carefully considered, but are unpersuasive. The amendment to claim 37 fails to obviate the rejection of record. The claims are drawn to constructs that "comprise" a galactose, and the method of Mattes results in the addition of a moiety that "comprises" a galactose. Furthermore, it is also noted that the specification teaches galactosylation of an antibody-enzyme fusion construct using the method of Mattes (see page 30).

Applicant also appears to be arguing that because Mattes teaches galatosylation of an antibody and not an antibody-enzyme fusion construct, that success making the construct cannot be predicted from Mattes. Applicant cites support for this assertion in Mattes by citing column and line number. However, this citation does not appear to correspond to the Mattes document that is cited, which does not contain column and line numbers, but only page numbers. Therefore, there does not appear to be any teaching in Mattes that teaches away from galactosylating an antibody-enzyme fusion construct.

The rejection is maintained because Seeman teaches the fusion glycoproteins comprising antigen binding fragments of the BW431/26 antibody conjugated or fused to β-glucuronidase, and because Mattes teaches how to galatosylate an antibody and why it would be desirable to galatosylate and antibody. Mattes teaches that increased clearance from the blood of antibodies

is desirable in order to reduce reactivity of the monoclonal antibodies in areas away from the tumor (in this case outside of the peritoneal cavity; see page 860; Discussion). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Seemann with that of Mattes to alter fusion proteins of Seemann by the addition of a galactose so that the fusion proteins are more rapidly cleared from the blood. One would have been motivated to modify the fusion proteins of Seemann in order to increase the relative tumor to blood ratio, which would be achieved if antibody-enyzme conjugates or fusion proteins are rapidly cleared from the blood.

7. The rejection of claims 37, 38, 40, 41, 43, 47, 54, 58, 66 and 67 under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; cited in IDS;) in view of Mattes (U.S. Patent 4,859,449; issued 08/1989) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976) is maintained for the reasons of record.

Applicant's arguments have been carefully considered but fail to persuade. Applicant argues that because Winkelhake teaches that intermediate degradation of sugars results in intermediate effects on antibody clearance that Winkelhake provides evidence concerning the unpredictability in the art of making galactosylated antibodies. This argument is unpersuasive because the claims read on galactosylated constructs and Winkelhake teaches that if degradation is complete and exposes the pentultimate galatose residue that blood clearance is more rapid. Nothing in Winkelhake teaches that there would be any uncertainty in the process because one were trying to make a galactosylated antibody versus a galactosylated antibody-enzyme

construct. Therefore, the grounds of rejection are maintained, because the prior art as a whole teaches the claimed inventions.

Seemann teaches glycoprotein fusion proteins and conjugates that comprise antibody binding fragments of BW431/26 monoclonal antibody linked to a β-glucuronidase, and teaches such fusion proteins and conjugates in methods for targeted prodrug activation at tumors. Seemann fails to teach glycoprotein fusion proteins or conjugates that comprise an exposed galactose, mannose, N-acetylglucosamine, lactose, N-acetyllactose, glucose or fucose. However, it is well known in the art to modify antibodies by either adding a sugar such as galactose by chemical means or by enzymatically degrading sialated carbohydrate groups using enzymes such as neuraminidase to expose sugars such as galactose. Mattes teaches chemical methods for addition of galactose or glucose to an anti-CEA antibody for increased clearance (col. 7, lines 6-col. 8, line 8). Mattes also teaches enzymatic methods of carbohydrate degradation (col. 6, lines 47-64). Winkelhake teaches methods of enzymatic degradation (page 1075, 2nd col.). Both Mattes and Winkelhake teach the increased clearance of modified antibodies is via the Ashwell receptors (asialoglycoprotein receptors) in the liver that recognize sugars such as galactose or mannose. Mattes teaches the desirability of increased clearance of therapeutic antibodies from the blood for the purpose of reducing side effects of antibodies or antibody conjugates caused by the presence of the antibody or antibody conjugate in the circulation. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the glycoprotein fusion proteins and conjugates of Seeman by adding a sugar such a galactose using the methods of Mattes or by enzymatic degradation to remove sialic acid using the methods of Winkelhake for the purpose of increasing clearance from the circulation.

8. The rejection of claims 37 and 56 under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; cited in IDS;) in view of Mattes (U.S. Patent 4,859,449; issued 08/1989) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976) and further in view of Bosslet (Bosslet et al, Br. J. Cancer 65: 234-238, 1992) and Jahde (Jahde et al, Cancer Res. 52: 6209-, 1992; abstract only) is maintained for the reasons of record.

Applicants' arguments have been carefully considered, but fail to persuade. Applicants assert that there is no motivation in the prior to combine the teachings of cited references. This is unpersuasive, because Bosslet teaches that as the pH is decreased the activity of β-glucuronidase increases, and Jahde teaches that it is well known to increase the therapeutic index of anticancer agents by inducing pH differences between malignant and normal tissues. Therefore, one of skill in the art would have been motivated to increase the activity of β-glucuronidase at the site of a tumor by adding an agent that lowers the pH of tumor cells.

Claims 37 and 56 are drawn to kits comprising fusion glycoproteins or conjugates comprising antibody or an antibody binding fragment thereof, fused or conjugated to an enzyme, where the antibody is the BW431/26 antibody, and a prodrug, and further comprising a pharmaceutical carrier the comprises an agent for lowering the intracellular pH of tumor cells. The enzyme portion of the fusion glycoprotein or conjugate may be β-glucuronidase. Seemann in combination with either Mattes or Winkelhake teaches a fusion glycoprotein or conjugate having an exposed carbohydrate moiety such as galactose. None of Seeemann, Mattes or Winkelhake teaches the further addition of an agent that lowers the intracellular pH of tumor cells. However, Bosslet teaches that β-glucuronidase increases in activity with a pH lower than

the physiological pH (page 236, 2nd col.). Jahde teaches methods of lowering intracellular pH. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included an agent for lowering the intracellular pH of tumor cells. One would have been motivated to include such an agent, because of the teachings of Bosslet demonstrating that the enzymatic activity of β-glucuronidase is increased at a pH that is lower than physiological pH.

9. The rejection of claims 37, 54 and 55 under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; cited in IDS;) in view of Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976) and further in view of Page (U.S. Patent 5,545,405; issued 08/1996; filed 10/1991) is maintained for the reasons of record.

Applicant argues that the fact that the prior art teaches that antibodies may be made in CHO cells is irrelevant to invention as a whole and that is no motivation for using CHO cells to make antibody fusion constructs. However, Page provides motivation for using CHO cells to make antibody constructs. For example, the CHO cells of Page enable the balanced expression of light and heavy chains and that balanced expression is desirable given that the light and heavy chains are linked together in the antibody molecule in equimolar proportions (see col. 2, lines 62-66) and the CHO cells of Page may be used to make all kinds of antibodies (see col. 3, lines 19-50).

Seemann teaches a recombinantly made fusion glycoprotein comprising the antigen binding fragment of the monoclonal antibody BW431/26 made in BHK cells. Seemann in combination with Winkelhake teaches a fusion glycoprotein that comprises an exposed galactose

residue. Seemann in combination with Winkelhake fails to teach a fusion glycoprotein that is made in CHO cells. However, the use of CHO cells to make antibodies is known in the art as evidenced by the disclosure of Page (col. 2, line 51- col. 6, line 26). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Seemann by using the methods of Page to make fusion glyocproteins in CHO cells.

10. The rejection of claims 37 and 57 under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; cited in IDS;) in view of Mattes (U.S. Patent 4,859,449; issued 08/1989) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976) and further in view of Bagshawe (U.S. Patent 5,632,990; issued 05/1997; filed 12/1990) is maintained for the reasons of record.

Applicant argues that the prior art merely provides an invitation to experiment, but does not provide an expectation of success. This argument is not persuasive, because the receptors that Bagashawe teaches the desirability of blocking are galactose receptors, thus one would have a reasonable expectation of success in blocking galactose receptors with the addition of galactose.

Claims 37 and 57 are drawn to kits that further comprise galactose in a pharmaceutical carrier. The combination of Seemann with Mattes or Winkelhake fails to teach fusion glycoproteins comprsing an exposed galactose residue in combination with galactose. However, Bagshawe teaches the use of galactosylated antibody constructs for the purpose of increased clearance and further teaches methods that comprise the additional use of a substance for

blocking galactose residues for the purpose of maintaining a high level of conjugate in the plasma until the galactose receptors are again free to take up the galactosylated conjugate. Bagshawe teaches that asialofetuin binds strongly to galactose receptors but that less immunogenic substances may be identified (col. 4, lines 33-41). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included galactose in the claimed kits for the purpose of temporarily decreasing clearance of the fusion glycoproteins or conjugates. One of ordinary skill in the art would have had a reasonable expectation of success in using galactose as a substance for temporarily decreasing clearance of the fusion glycoproteins or conjugates because the receptors are galactose receptors.

11. The rejection of claims 37-43, 47, and 54-58 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for the reasons of record. The basis for this rejection is that, to the extent the claims read on fusion glycoproteins that comprise the entire specific monoclonal antibody BW431/26 (and on claims of using said fusion glycoprotein), the specification fails to describe how to make this one species, because the specification fails to indicate that the specific monoclonal antibody BW431/26 has been deposited with all restrictions removed, or that this specific monoclonal antibody is publically available, or that the amino acid sequence of the entire monoclonal antibody is publically available. A review of the references cited in the application demonstrates that the nucleotide and amino acid sequences of the variable domains of the light and heavy chains are known in the art. However, sequences of the variable

domains are not equivalent to the sequences of the entire molecule that is the specific monoclonal antibody, BW431/26. Therefore, the rejection is maintained.

Reproduction of an identical monoclonal antibody is an unpredictable event. Because it does not appear that the BW431/26 monoclonal antibody is publicly available or can be reproducibly isolated from nature without undue experimentation, one of ordinary skill in the art cannot be assured of the ability to practice the entire scope of the claimed inventions. Because claims 37-43, 47, and 54-58 specifically require the use of the BW431/26 monoclonal antibody, a suitable deposit of the hybridoma producing the BW431/26 monoclonal antibody is required, or evidence must be provided that the BW431/26 monoclonal antibody is well known and readily available to the public, or that it is reproducible without undue experimentation.

Furthermore, unless a deposit was made at or before the time of filing, a declaration filed under the 37 C.F.R. 1.132 is necessary to construct a chain of custody. The declaration, executed by a person in a position to know, should identify the deposited hybridoma by its depository accession number, establish that the deposited hybridoma is the same as that described in the specification, and establish that the deposited hybridoma was in applicant's possession at the time of filing. Applicant is required to amend the specification to recite the accession number of the deposit, the date of deposit, a description of the deposited biological material, and the name and address of the depository. See In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

If the deposit is made under the provision of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number

stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the Budapest Treaty as the treaty leaves this specific matter to the discretion of each member state.

If the deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit, over his or her signature and registration number, averring:

(a) that all restrictions on the availability to the public of the material will be irrevocably removed upon the granting of a patent.

(b) that the material has been deposited under conditions that ensure that access to the material will be available during the pendancy of the patent application to one determined by the Commissioner to be entitled thereto under 35 CFR 1.14 and 35 USC 122.

(c) that the deposited material will be stored with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case at least thirty (30) years after the date of a deposit or for the enforceable life of the patent, whichever is longer.

(d) that the duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit.

New Grounds of Rejection:

The following new grounds of rejection were necessitated by the amendment.

12. Claim 47 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 47 was previously objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants argue that this objection should be withdrawn because claim 37, from which claim 47 depends, is drawn to a fusion constructs which comprise a BW431/26 antibody or antigen binding fragment thereof, and therefore, reads on constructs that bind to more than one tumor antigen. However, applicants have failed to demonstrate support for such a genus of compounds, either any construct that binds to more than one tumor antigen or to the subgenus of constructs that comprise aa BW431/26 antibody or antigen binding fragment thereof and also bind a second tumor antigen. Therefore, claim 47 adds new matter to the specification and lacks written description.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
October 15, 2003

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